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(54) Title: CYCLOALKYL–CARBOXYLIC ACID ESTERS OF 7.ALPHA.METHYL–ESTR–4–EN–3–ONE 17.BETA.–OL (19–NOR 7.ALPHA.–METHYLTESTOSTERONE)

(57) Abstract

The invention is the novel androgen (7α,17β)–17–[[(*trans*–4–butylcyclohexyl)carbonyl]oxy]–7–methylestr–4–en–3–one (MENT buciclate) and related cycloalkyl esters. This compound distinguishes favourably from other testosterone derivatives in that it has a good solubility in oily media. It particularly exhibits a good dissolved potency relative to testosterone. The compound is particularly suitable for administration by means of injection.

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CYCLOALKYL-CARBOXYLIC ACID ESTERS OF 7.ALPHA.METHYL-ESTR-4-EN-3-ONE 17.BETA.-OL (19-NOR 7.ALPHA.-METHYLTESTOSTERONE)

The invention is in the field of androgenic hormones, more specifically derivatives of testosterone.

Testosterone derivatives are known. Testosterone itself, the natural male hormone, has many known drawbacks as far as methods of administration are concerned. It has a short-lasting activity, is insoluble in the usual pharmaceutically acceptable media, and is not very potent. The more potent dihydrotestosterone (5α-reduced form of testosterone) is considered a health-risk, notably for the prostate.

More potent androgens are 7α-methyl-19-nortestosterone (MENT) and related compounds, such as disclosed in FR 4.521 M and US 5,342,834. However, MENT suffers from a bad solubility and short duration of action.

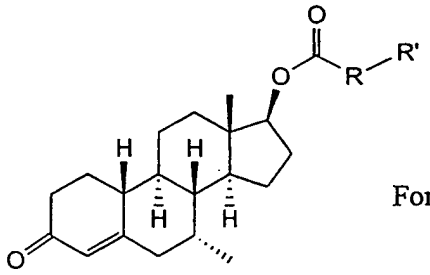
As androgens having an improved duration of action, the cycloalkyl esters of testosterone have been disclosed in US 4,948,790. These, however, are neither very potent, nor sufficiently soluble, and lead to too low plasma levels of testosterone than are feasible.

New androgenic hormones are needed which *inter alia* satisfy the demands connected with new areas of interest, such as male contraception and male HRT (hormone replacement therapy). Thus, *e.g.*, male contraception may comprise a regimen of administration of hormones in which a progestagen serves to achieve a contraceptive effect and an androgen serves to supplement the resulting decreased testosterone level. Another option is that male contraception is performed with an androgenic hormone alone. The regular androgen intake needed for this requires androgens which are improved as to potency and duration of action, and for which a practical way of administration is available. As low a frequency of administration being desired, there is a demand for androgens which have such physico-chemical properties as to be rendered into a solution, particularly a solution by which the androgen can be administered via injection, preferably once a week or less frequent, or orally via a capsule to be taken, *e.g.* daily. This means that a basic desired property for a novel

androgen is that it has an improved solubility in one or more pharmaceutically acceptable liquids.

Even more desired is an androgen which has a favourable relationship of potency and solubility, as a weak androgen will require more of it to be dissolved in order to attain the same activity than in the case of a more potent androgen. This means an androgen having an improved relative "dissolved potency", hereinafter referred to as RDP, wherein the RDP of a given androgen in a given medium is the product of its androgenic potency relative to that of the natural male hormone testosterone and its solubility in the medium relative to that of testosterone.

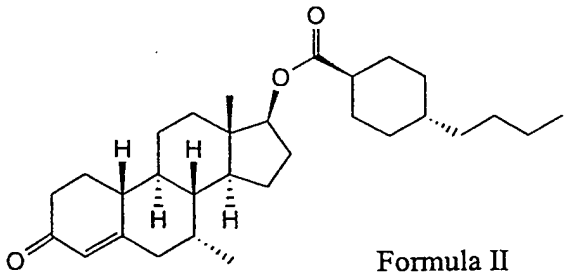
It is an object of the invention to provide an androgenic hormone which satisfies the above demand. According to the invention, this is achieved by a compound of the general formula I



Formula I

wherein R stands for cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl and R' is hydrogen or a straight chain or branched chain alkyl group of 2-6 carbon atoms.

In a preferred embodiment, the invention is the compound (7α,17β)-17-[[(*trans*-4-butylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one, which has the following structural formula II:



Formula II

This preferred compound of the invention is also to be referred to as 7α-methyl-19-nortestosterone buciclate, in short MENT buciclate.

The compounds of the invention have a significantly better solubility than could be expected on the basis of the known testosterone derivatives, including MENT. Moreover, the compounds of the invention have a surprisingly higher RDP than the known compounds.

The compounds of the invention can be prepared by esterification of the 17-OH group of MENT with a suitable carboxylic acid or carboxylic acid derivative, such as, in the case of the preferred compound, *trans*-4-butylcyclohexanecarboxylic acid or derivatives thereof. This esterification may be carried out using methods well known in the art or readily available from the chemical literature, for example, using methods and catalysts described in Advanced Organic Chemistry, J. March, 4th Ed, pages 1281-1282, 1992, or analogously with the compounds disclosed in US 4,948,790. MENT can be prepared as disclosed in FR 4.521 M and US 5,342,834.

The invention also pertains to each of the above compounds, and particularly MENT buciclate, as a medicine. The compounds of the invention being potent androgens, they can be used in, *inter alia*, male contraception and male or female hormone replacement therapy. Thus the invention also pertains to a method of treatment of androgen insufficiency, by administering to a human male or female an effective amount of a compound of the invention, such as MENT buciclate. The invention also is in the use of of a compound of the invention, such as MENT buciclate for the preparation of a medicine for treating androgen insufficiency. In the context of the invention, the term "androgen insufficiency" is to be understood to pertain to all kinds of diseases, disorders, and symptoms in which a male or a female suffers from too low a testosterone level, such as in hypogonadal men. In particular, the androgen insufficiency to be treated by the compound of the invention is the reduction of the testosterone level which a human male incurs as a result of age (the compound of the invention is then used for male hormone replacement therapy), or when he is subject to male contraception. In the context of male contraception, the compound of the invention especially serves to neutralise the effect of regimens of male hormone contraception in which a

sterilitant such as a progestagen or LHRH (luteinizing hormone releasing hormone) is administered regularly, *e.g.* daily, or it is used as the sole male contraceptive substance.

The invention also relates to pharmaceutical formulations comprising a compound of the invention, such as MENT buciclate and a pharmaceutically acceptable carrier. Thus the carrier may be in a solid form or liquid form, and the formulation may be an oral dosage unit such as a tablet or, preferably, an oral solution, *e.g.* in a capsule. Methods and compositions for making such dosage units are well-known to those skilled in the art. For example, conventional techniques for making tablets and pills, containing active ingredients, are described in the standard reference, Gennaro *et al*, Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture). The compound can also be administered via an implant, a patch, or any other suitable device for the sustained release of an androgen composition. The preferred oral dosage unit is that of a capsule containing the compound of the invention taken up in a liquid medium as described below.

In order to benefit most from the compound's androgenic activity, administration of the compound dissolved in an oil is preferred, *i.e.* either orally as above, and notably via (intramuscular) injection. The compounds of the invention, and notably MENT buciclate, have a solubility in oily media, which makes them particularly suitable for a liquid pharmaceutical formulation comprising a compound as defined above, and preferably MENT buciclate, dissolved in a pharmaceutically acceptable oil. Suitable oils are, *e.g.* arachis oil, oleic acid, ricinus oil, sesam oil and the like. Arachis oil is preferred.

For injection the preferred injection device is a needleless injection system, *e.g.* as described in US 5,599,302. To this end the compound may also be suspended in an aqueous medium, but the above solutions in oil are preferred. Methods and compositions for making liquids suitable for parenteral administration are known in the art, see *e.g.* Remington's, pages 1545 ff.

For oral administration, any capsule made from a pharmaceutically acceptable wall material can be employed. Methods and compositions for making capsules suitable for oral

administration are known in the art, see *e.g.* Remington's, pages 1658 ff. A preferred material is a softgel such as used for Andriol® capsules.

The invention also pertains to a method of treatment of androgen insufficiency, by administering to a human male, by injection or by means of an oral dosage unit, an effective amount of MENT buciclate dissolved in a pharmaceutically acceptable oil. The invention also is in the use of MENT buciclate for the preparation of a medicine for treating androgen insufficiency by injecting into a human male an effective amount of MENT buciclate dissolved in a pharmaceutically acceptable oil, or by orally administering such an oily solution.

The dose of and regimen of administration of the compounds as defined above, or a pharmaceutical composition thereof, to be administered will obviously depend on the therapeutic effect to be achieved and will vary with the route of administration, and the age and condition of the individual subject to whom the medicament is to be administered, and/or or the particular contraceptive or HRT regimen in which it is used. Typical doses are 100 mg or more per three months upon intramuscular administration and 50-250 mg, more preferably 80 mg per day upon oral administration.

The invention will be further explained hereinafter with reference to the following Examples and Figures.

Figure 1

A graphic representation of the relative "dissolved potency" RDP in arachis oil of testosterone (1), MENT (2), testosterone buciclate (3), and MENT buciclate (4).

Figure 2

A graphic representation of the relative "dissolved potency" RDP in oleic acid of testosterone (1), MENT (2), testosterone buciclate (3), and MENT buciclate (4).

EXAMPLE 1

(7α,17β)-17-[[(*trans*-4-Butylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one.

i) - A total of 8 grams of commercially available *trans*-4-butylcyclohexanecarboxylic acid were added to 9.5 ml of thionyl chloride and the reaction mixture was stirred overnight at ambient temperature. The excess of thionyl chloride was evaporated under reduced pressure to yield 8.80 g of *trans*-4-butylcyclohexanecarbonyl chloride.

ii) - At 0-5° C, 2.23 g (11 mmol) of this crude *trans*-4-butylcyclohexanecarbonyl chloride were added to a stirred solution of 1.58 g (5.5 mmol) of (7α,17β)-17-hydroxy-7-methylestr-4-en-3-one in 16 ml of pyridine. The reaction mixture was allowed to reach room temperature and was stirred overnight. Thereafter, ice was added and after stirring for another 2 hours, the reaction mixture was poured into ice-water, containing 80 ml of 2 N HCl, followed by ethyl acetate extraction. The organic layers were washed with water, cold 1 N NaOH solution and brine, dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was chromatographed over silica. Elution with heptane-ethylacetate (4:1) and evaporation gave a crystalline residue. Collection of the crystals yielded 1.4 g of MENT buciclate, *i.e.* (7α,17β)-17-[[(*trans*-4-butylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one, m.p. 66 °C, $[\alpha]_D^{20}$ = +50° (c = 1; dioxane), MS (ESI): 454.

EXAMPLE 2

Following procedures analogous to those described under Example 1, and using (7α,17β)-17-hydroxy-7-methylestr-4-en-3-one and an appropriate (alkyl)cycloalkylcarboxylic acid as starting materials, the following products were prepared:

a) - (7α,17β)-17-[(Cyclopropylcarbonyl)oxy]-7-methylestr-4-en-3-one, m.p. 98-99 °C.

b) - (7α,17β)-17-[[(2-Hexylcyclopropyl)carbonyl]oxy]-7-methylestr-4-en-3-one (mixture of 2 diastereomers, ratio 2:1), $[\alpha]_D^{20}$ = +45.0 ° (c = 0.35; dioxane).

c) - (7α,17β)-17-[(Cyclobutylcarbonyl)oxy]-7-methylestr-4-en-3-one, $[\alpha]_D^{20}$ = +46.0 ° (c = 1; dioxane).

d) - (7α,17β)-7-Methyl-17-[[(3-pentylcyclobutyl)carbonyl]oxy]estr-4-en-3-one (mixture of 2 diastereomers, ratio 1:1), $[\alpha]_D^{20}$ = +41.5 ° (c = 0.6; dioxane).

e) - (7α,17β)-7-Methyl-17-[[(3-pentylcyclopentyl)carbonyl]oxy]estr-4-en-3-one (mixture

of 2 diastereomers, ratio 4:1), $[\alpha]_D^{20}$ = +36.0 ° (c = 0.45; dioxane).

f) - (7α,17β)-17-[[(*cis*-4-Ethylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one, m.p. 90 °C.

g) - (7α,17β)-17-[[(*trans*-4-Ethylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one, m.p. 117-119 °C.

h) - (7α,17β)-7-Methyl-17-[[(*cis*-4-propylcyclohexyl)carbonyl]oxy]estr-4-en-3-one, $[\alpha]_D^{20}$ = +37.2 ° (c = 0.5; dioxane).

i) - (7α,17β)-7-Methyl-17-[[(*trans*-4-propylcyclohexyl)carbonyl]oxy]estr-4-en-3-one, m.p. 89-91 °C.

j) - (7α,17β)-17-[[(*cis*-4-Butylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one, $[\alpha]_D^{20}$ = +40.0 ° (c = 1; dioxane).

k) - (7α,17β)-17-[[[(*cis*)-4-(1,1-Dimethylethyl)cyclohexyl]carbonyl]oxy]-7-methylestr-4-en-3-one, m.p. 150 °C.

l) - (7α,17β)-17-[[[(*trans*)-4-(1,1-Dimethylethyl)cyclohexyl]carbonyl]oxy]-7-methylestr-4-en-3-one, m.p. 132-135 °C.

m) - (7α,17β)-7-Methyl-17-[[(*cis*-4-pentylcyclohexyl)carbonyl]oxy]estr-4-en-3-one, $[\alpha]_D^{20}$ = +40.0 ° (c = 1; dioxane).

n) - (7α,17β)-7-Methyl-17-[[(*trans*-4-pentylcyclohexyl)carbonyl]oxy]estr-4-en-3-one, m.p. 81-83 °C.

o) - (7α,17β)-17-[[(*cis*-4-Hexylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one, $[\alpha]_D^{20}$ = +37.1 ° (c = 1; dioxane).

p) - (7α,17β)-17-[[(*trans*-4-Hexylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one, m.p. 79-82 °C.

EXAMPLE 3

(17β)-17-[[(*trans*-4-Butylcyclohexyl)carbonyl]oxy]androst-4-en-3-one.

The title compound (*i.e.* testosterone buciclate) was prepared from 1.58 g of (17β)-17-hydroxyandrost-4-en-3-one and 2.23 g of *trans*-4-butylcyclohexanecarbonyl chloride following procedures analogous to those described under Example 1. Yield 1.3 g, m.p. 133° C, $[\alpha]_D^{20}$ = +81° (c = 1; dioxane), MS (ESI): 454.

EXAMPLE 4

About 20-30 mgs of compound were powdered and then dissolved in as little solvent as necessary to dissolve all the visible particles. Dissolution was accomplished by heating in a waterbath of 50 °C and shaking on a Vortex™ shaker for 15 minutes. The solubility was calculated by determining the amount of compound (in mg) dissolved per ml of solvent. Results are collected in the table below.

COMPARATIVE EXAMPLE

The solubility and the androgenic potency of MENT buciclate and three reference compounds was used to determine RDP. The results are given in the Figures. With regard to clinically desirable anabolic and antigonadotropic effects (androgenic effects), MENT is ten times more potent than testosterone in rats (Kumar N et al, Endocrinology 130: 3677-3683 (1992) and J Steroid Biochem Molec Biol 52: 105-112 (1995)) and monkeys (Cummings D et al, J Clin Endocrinol Metab 83, 4212-4219 (1998)). The RDP is determined as follows:

$$\frac{\text{Solubility of compound}}{\text{Solubility of testosterone}} \times \text{potency of compound relative to that of testosterone}$$

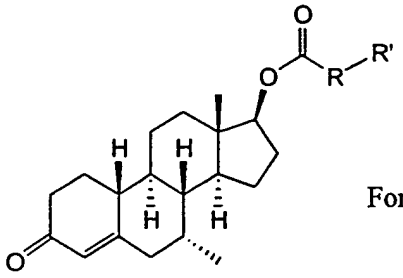
Table. Solubility of testosterone, MENT, testosterone buciclate, and compounds of the invention in arachis oil and in oleic acid.

Compound/ Example	solubility in arachis oil (mg/ml)	solubility in oleic acid (mg/ml)
testosterone	<< 0.1	~ 25
MENT	≤ 0.1	~ 15
testosterone buciclate (Ex. 3)	1-2	~ 50-60
MENT buciclate (Ex. 1)	~ 10	~ 50
Example 2a	8	25
Example 2b	> 200	> 250
Example 2c	5	15
Example 2d	300	160
Example 2e	> 250	> 200
Example 2f	50	< 10
Example 2g	10	25
Example 2h	65	< 10
Example 2i	10	30
Example 2j	50	100
Example 2k	15	< 10
Example 2l	5	10
Example 2m	40	100
Example 2n	15	50
Example 2o	40	100
Example 2p	10	30

From the table it can be learned that the solubility of MENT buciclate and the other compounds of the invention in arachis oil is much better than that of testosterone, MENT, and testosterone buciclate. The solubility of MENT buciclate and most of the other compounds of the invention in oleic acid is also better than expected in view of that of the known androgens.

Claims

1. A compound of the structural formula I:



Formula I

wherein R stands for cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl and R' is a hydrogen or a straight chain or branched chain alkyl group of 2-6 carbon atoms.

2. The compound (7α,17β)-17-[[(*trans*-4-butylcyclohexyl)carbonyl]oxy]-7-methylestr-4-en-3-one (MENT buciclate).

3. A compound of the structural formula I as a medicine.

4. MENT buciclate as a medicine.

5. The use of a compound of the structural formula I for the preparation of a medicine for treating androgen insufficiency.

6. The use of MENT buciclate for the preparation of a medicine for treating androgen insufficiency.

7. A pharmaceutical formulation comprising a compound of the structural formula I and a pharmaceutically acceptable carrier.

8. A pharmaceutical formulation comprising MENT buciclate and a pharmaceutically acceptable carrier.

9. A pharmaceutical formulation according to claim 7 or 8, characterised in that the carrier is a liquid in which MENT buciclate is dissolved.

10. A kit for male contraception comprising means for the administration of a progestagen and means for the administration of an androgen, characterised in that the latter means is a pharmaceutical formulation according to claim 7 or 8.

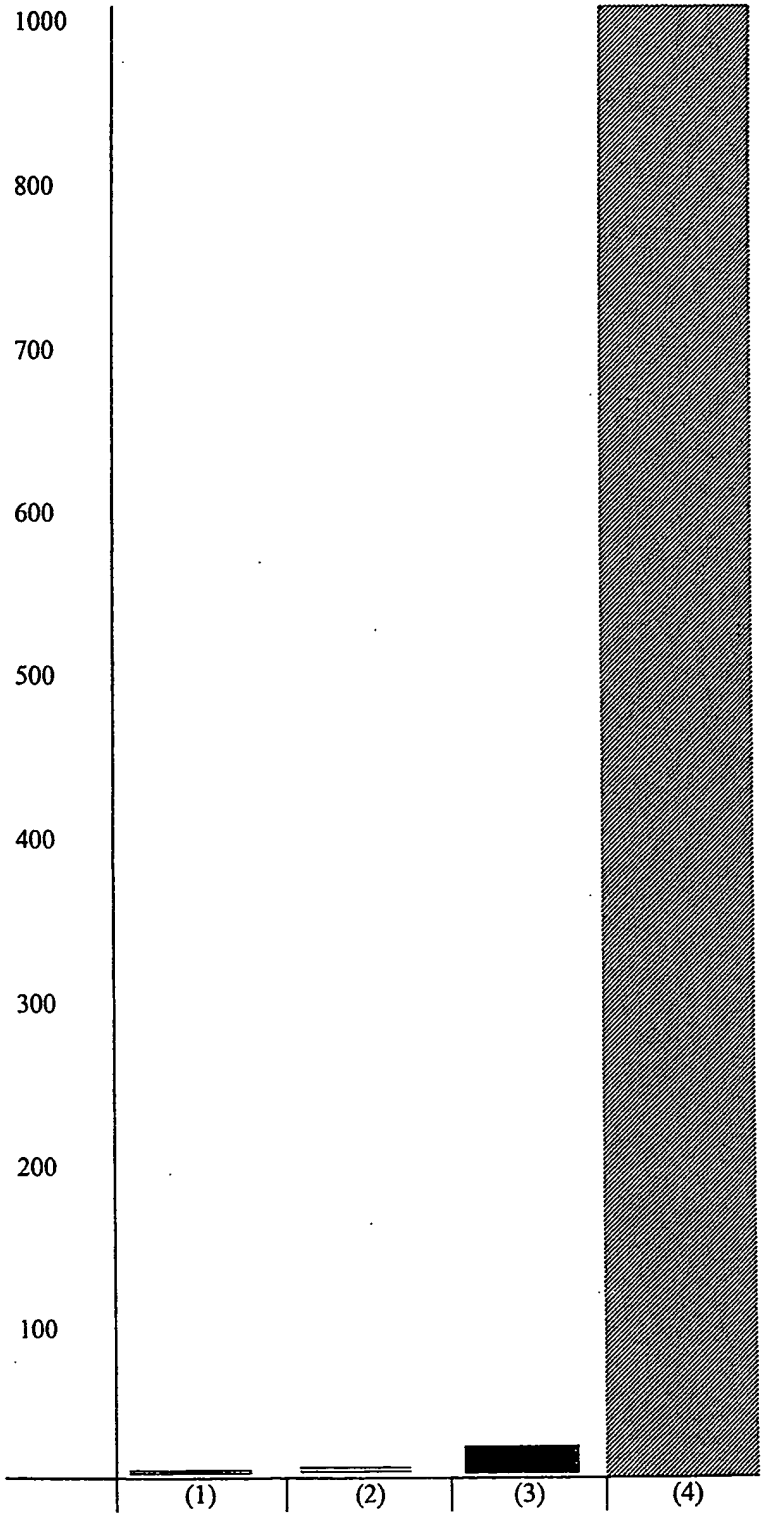


FIG.1

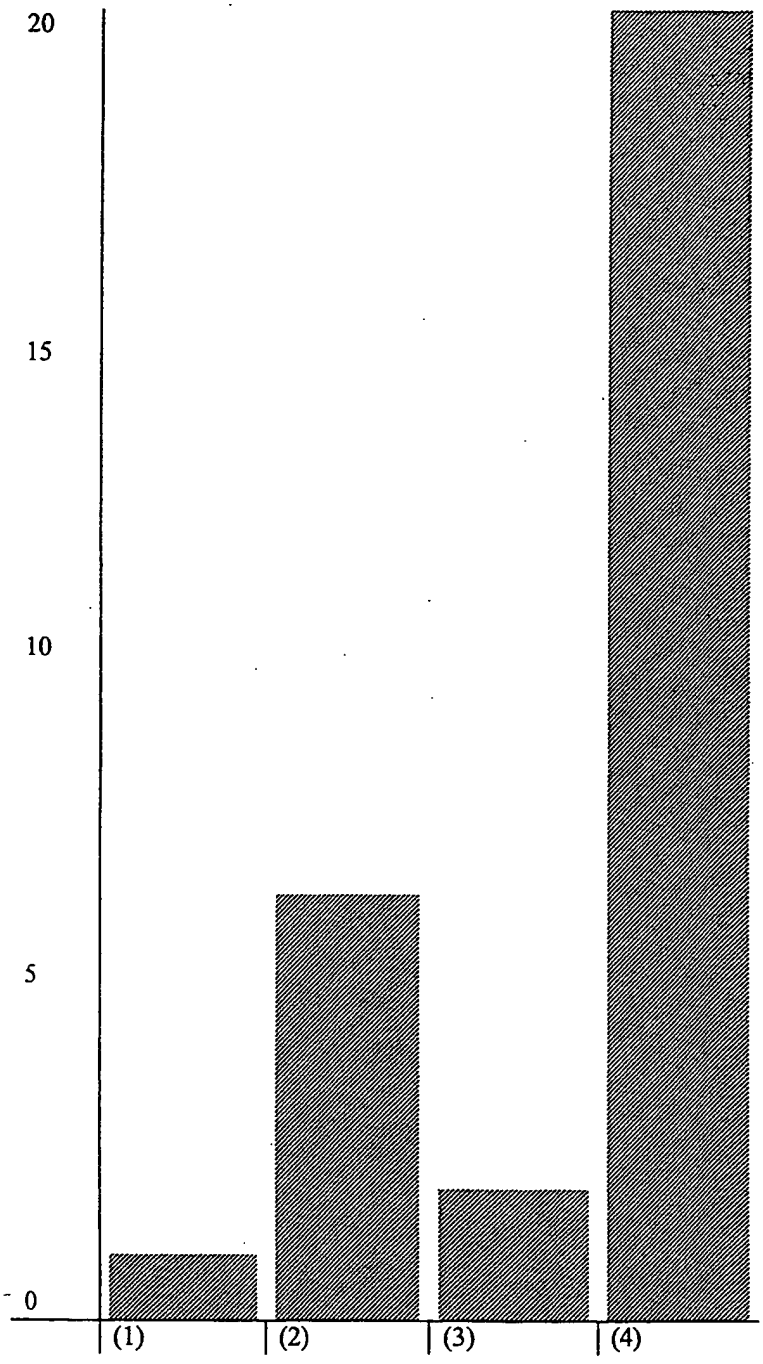


FIG.2

INTERNATIONAL SEARCH REPORT

Inte tional Application No
P[redacted] 99/04101

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07J1/00 A61K31/565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HUNT W L ET AL: "Sexual activity in castrated male rabbits after oral administration of 7.alpha.-methyl-19-nortestosterone 17-(1-adamantoate)" PHYSIOLOGY AND BEHAVIOR, vol. 11, no. 6, 1973, pages 893-896, XP002082863 the whole document	1-10
Y	US 5 342 834 A (BARDIN C WAYNE ET AL) 30 August 1994 (1994-08-30) cited in the application column 2, line 11 - line 20 column 2, line 39 - line 40	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 September 1999	27/09/1999

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 948 790 A (ARCHER SYDNEY ET AL) 14 August 1990 (1990-08-14) cited in the application column 2, line 18 - line 32; examples I,III,IV column 2, line 65 - line 68	1-10
Y	RAJALAKSHMI M ET AL: "Effect of two new androgen esters on serum levels of testosterone in castrated rhesus monkey" CONTRACEPTION, vol. 42, no. 2, 1990, pages 235-240, XP002082864 the whole document	1-10
Y	MATLIN, S. A. ET AL: "Long-acting androgens: analytical and preparative HPLC of testosterone esters" JOURNAL OF HIGH RESOLUTION CHROMATOGRAPHY AND CHROMATOGRAPHY COMMUNICATIONS., vol. 10, no. 4, April 1987 (1987-04), pages 186-190, XP002115189 DR.ALFRED HUETHIG VERLAG. HEIDELBERG., DE ISSN: 0935-6304 the whole document	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
P[redacted]P 99/04101

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5342834 A	30-08-1994	NONE	
US 4948790 A	14-08-1990	NONE	